ORGANIC LETTERS

2012
Vol. 14, No. 7
1684–1687

Expedient Construction of the [7−5−5] All-Carbon Tricyclic Core of the Daphniphyllum Alkaloids Daphnilongeranin B and Daphniyunnine D

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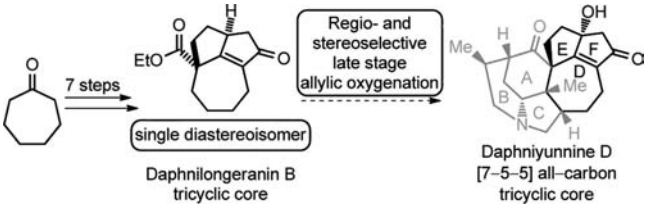
Received January 27, 2012

ABSTRACT



A synthetic strategy for the construction of the [7−5−5] all-carbon tricyclic core of numerous calyciphylline A-type Daphniphyllum alkaloids has been developed using a key intramolecular Pauson−Khand reaction. A subsequent base-mediated double-bond migration and a regio- and stereoselective radical late stage allylic oxygenation provide access to the substitution patterns of daphnilongeranin B and daphniyunnine D.

One of the major challenges in the total synthesis of the architecturally complex and biologically interesting Daphniphyllum alkaloids[1] is the construction of the DEF ring system, the [7−5−5] all-carbon tricyclic core. This complex motif is present in approximately half of the family of over 200 molecules. Of particular interest to our group is the calyciphylline A-type subclass due to their unique structural features, biological activity, and the lack of reports of the total synthesis of any of its members.[2]

Calyciphylline A (**1**)[3] and nine other related natural products bearing this [7−5−5] fused ring system are represented in Figure 1: daphnipaxianine A−C (**8**, **9**, **5**),[4]

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10.1021/ol3002267
Published on Web 03/09/2012

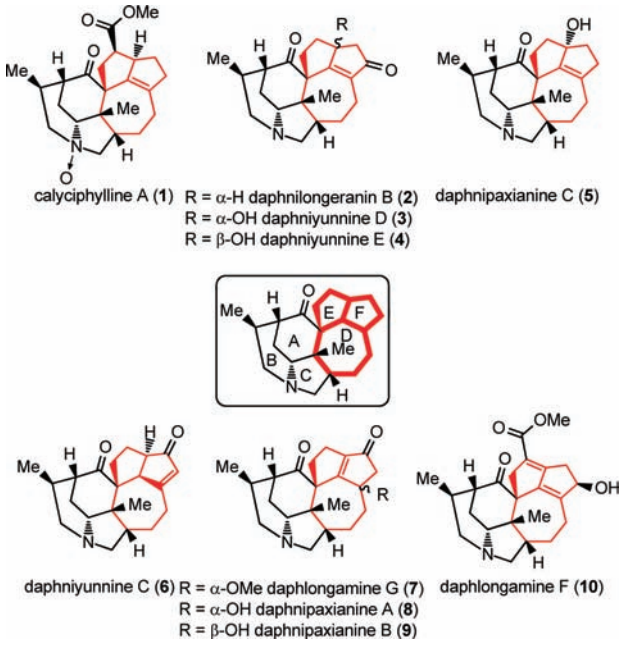


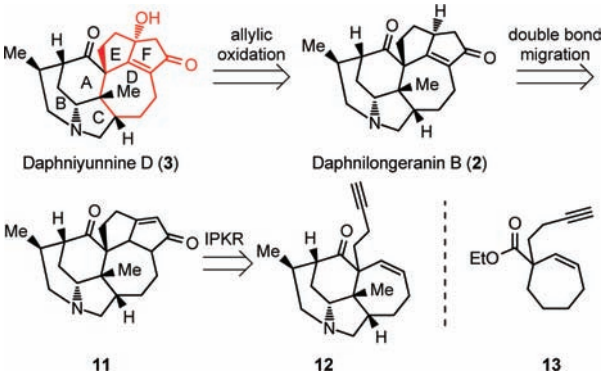
Figure 1. *Daphniphyllum* alkaloids bearing the [7−5−5] all-carbon tricyclic core.

daphlongamine F and G (**10**, **7**),[5] daphnilongeranin B (**2**),[6] daphniyunnine C−E (**6**, **3**, **4**).[7] Although direct synthetic approaches toward the [6−5] bicycle (AC rings in Figure 1), [6−6−5] tricycle (ABC rings), and [6−5−7] tricycle (ACD rings) of this subgroup of alkaloids have been reported by our group[8] and others,[9] no specific study of a realistic endgame involving a synthesis of the aforementioned core of this subgroup has been reported.[10,11] For a successful total synthesis of any member of this subclass, a robust and practical route for the rapid assembly of this common structural motif is required. Herein we present our findings toward this aim.

Our retrosynthetic analysis focused on construction of the main tetracycle **12** in which the pendant terminal alkyne and cycloheptene functionalities provided an ideal entry to the DEF ring system (**11**) via the intramolecular Pauson−Khand reaction[12] (IPKR). In order to test our hypothesis and to demonstrate the possible versatility in the total synthesis of the resultant tricyclic core, we chose to target the cyclopentenone-containing portion of daphnilongeranin B (**2**) and daphniyunnine D (**3**), since the latter shows interesting cytotoxic activity against two tumor cell lines, P-388 and A-549, with IC_{50} values of 3.0 and 0.6 μM, respectively.[7]

For the synthesis of daphnilongeranin B (**2**), following the IPKR, we envisioned a double-bond migration to the most substituted and thermodynamically most stable cyclopentenone isomer (Scheme 1).[13] This novel two-step

Scheme 1. Retrosynthetic Analysis of Daphnilongeranin B and Daphniyunnine D



tandem strategy was a realistic alternative to a controlled late stage construction of a strained cycloheptyne moiety, necessary if a direct one-step IPKR approach was to be adopted.[14] A late stage regio- and stereoselective allylic oxygenation would provide the second target, daphniyunnine D (**3**).

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(14) For examples of IPKR performed on Co-complexed: (a) Cycloheptyne functionalities, see: Mohamed, A. B.; Green, J. R.; Masuda, J. *Synlett* **2005**, 1543–1546. (b) Cyclooctyne funtionalities, see: Jamison, T. F.; Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4353–4363.

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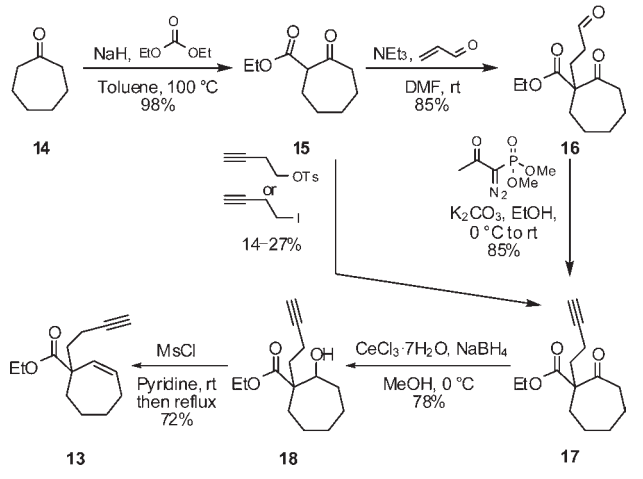
The use of the IPKR is growing in the synthetic community with examples of construction of a related all-carbon skeleton as well as oxygen, nitrogen, and sulfur containing [5−5−5],[15] [6−5−5],[16] [7−5−5],[10,14a,17] and [8−5−5][14b,17c] fused ring systems.[18] However, in order to test our proposal and to demonstrate the potential versatility of the construction of this all-carbon [7−5−5] tricyclic core, we focused our efforts on the construction of molecule **13** as a model substrate (Scheme 2).

Our route to the IPKR substrate **13** is presented in Scheme 2. The commercially available cycloheptanone **14** was readily transformed into ketoester **15**, in 98% yield, using sodium hydride and diethylcarbonate. A direct enolate alkylation approach for introducing the butyne side chain, using 1-but-3-ynyl tosylate and 4-iodobut-1-yne, was investigated and was partly successful; **17** was isolated, but only in 14−27% yield. Accordingly, we examined an alternative pathway for the introduction of the pendant alkyne, via a two-step sequence. First a Michael addition to acrolein[19] efficiently provided the aldehyde **16** in 85% yield. Subsequently, the Ohira−Bestmann modification[20] of the Seyferth−Gilbert homologation,[21] using ethanol[22] as solvent, afforded the alkyne **17** in 85% yield.

We then turned our attention to the preparation of the IPKR substrate from **17**. The attempted direct transformation of the ketone to the required alkene via a Shapiro reaction[23] only led to complex mixtures and prompted us to adopt a sequential route. Reduction of the ketone using the Luche conditions[24] in methanol gave **18** in 78% yield. Pleasingly, a one-pot mesylation of the alcohol in pyridine, followed by elimination, gave the desired IPKR substrate **13** in 72% yield.

Scheme 2. Synthesis of the IPKR Substrate **13**



Reacting **13** with the cheap and commercially available dicobalt octacarbonyl[25] transiently produced the cobalt−alkyne complex **19** which was subsequently subjected to a range of different conditions known to initiate the [2 + 2 + 1] cycloaddition (Table 1).[26] Boiling the complex in acetonitrile, in the absence of a promoter, gave **20** in an encouraging 43% yield (entry 1). Using DMSO, PhSMe, and $CyNH_2$ as promoters, however, only resulted in gradual degradation of the complex even at rt after 24 h with no evidence of product formation (entries 2−4). The use of an amine *N*-oxide promoter, trimethylamine *N*-oxide (TMANO), gave a 39% yield (entry 5), whereas NMO proved to be more effective giving the desired product in 44% yield (entry 6). Pleasingly, rapid purification of **19** by flash column chromatography (fcc) on silica gel prior to addition of the NMO led to further improvement; **20** was afforded in 58% yield (entry 7) with a 4:1 dr in favor of **20a**, the stereochemistry of which was determined by NOE experiments.

With the direct IPKR product **20** in hand, an investigation of the crucial migration of the carbon−carbon double bond to the more substituted position then followed.[13] While 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) and DBU in dichloromethane only gave traces and a 52% yield of product **21** respectively, potassium carbonate (K_2CO_3) in ethanol smoothly accomplished the transformation with an excellent 92% yield (Scheme 3). Much to our delight, only one diastereoisomer was obtained possessing the desirable relative stereochemistry present in the DEF rings of daphnilongeranin B (**2**).[27]

In order to further demonstrate the versatility of this IPKR strategy to access the typical [7−5−5] ring structures of the calyciphylline A-type alkaloids, we examined the allylic oxygenation of structure **21**. This late stage oxygenation would furnish the tricyclic substitution pattern of the targeted daphniyunnine D (**3**) and/or daphniyunnine E (**4**). Inspired by Corey's method for allylic oxidation,[28] use of stoichiometric Pearlmann's catalyst combined with K_2CO_3 and *t*-BuOOH in CH_2Cl_2 gave the desired product

(18) For more examples of tricyclic ring systems, see reviews in refs 12b−e and references cited therein.

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(22) Using methanol as solvent resulted in a mixture of the expected product and its transesterified analogue in 15% and 40% yields respectively.

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(26) For promoter studies using: (i) (a) Sulfoxides, see: Chung, Y. K.; Lee, B. Y.; Jeong, N.; Hudecek, M.; Pauson, P. L. *Organometallics* **1993**, *12*, 220–223. (ii) Sulfides, see: (b) Sugihara, T.; Yamada, M.; Yamaguchi, M.; Nishizawa, M. *Synlett* **1999**, 771–773. (iii) Primary amines, see: (c) Sugihara, T.; Yamada, M.; Ban, H.; Yamaguchi, M.; Kaneko, C. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2801–2804. (iv) Amine *N*-oxides, see: (d) Shambayati, S.; Crowe, W. E.; Schreiber, S. L. *Tetrahedron Lett.* **1990**, *31*, 5289–5292. (e) Jeong, N.; Chung, Y. K.; Lee, B. Y.; Lee, S. H.; Yoo, S.-E. *Synlett* **1991**, 204–206.

(27) The relative stereochemistry was determined by NOE experiments.

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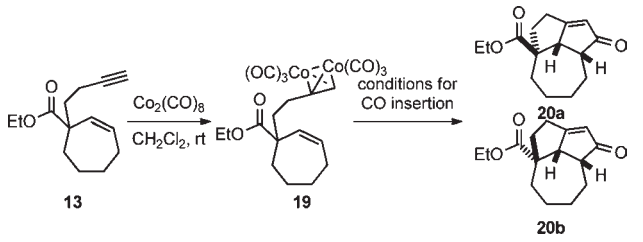
Table 1. Optimization of the IPKR

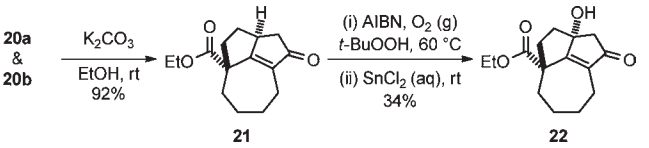


entry	solvent	promoter (equiv)	temp (°C)	time (h)	yield % (dr **20a:20b**)
1[a]	MeCN	heat	reflux	24	43 (4.0:1.0)
2	CH_2Cl_2	DMSO (6 equiv)	rt	24	0 (N/A)
3	CH_2Cl_2	PhSMe (6 equiv)	rt	24	0 (N/A)
4	CH_2Cl_2	$CyNH_2$ (6 equiv)	rt	24	0 (N/A)
5	CH_2Cl_2	TMANO[b] (9 equiv)	rt	24	39 (3.4:1.0)
6	CH_2Cl_2	NMO (9 equiv[c])	rt	24	44 (4.0:1.0)
7[d]	**CH_2Cl_2**	**NMO (9 equiv)**	**rt**	**22**	**58 (3.7:1.0)**

[a] CH_2Cl_2 from the initial step was removed under reduced pressure, and to the resultant dark colored oil was added MeCN. [b] Trimethylamine *N*-oxide. [c] An initial 6 equiv were added, followed by a further 3 equiv after 18 h. [d] The cobalt−alkyne complex formed in the initial step was purified by fcc before subjecting it to the stated conditions.

22 in a promising 20% yield (50% based on recovered starting material), demonstrating the possibility of this late stage functionalization of the fused tricyclic ring system. Employing the radical oxygenation conditions reported by Watt[29] as an alternative gave rise to **22** as a single regio- and stereoisomer in an acceptable 34% yield.[30]

Scheme 3. Synthesis of the Tricyclic Core **22**



In summary we report a robust and practical route for the rapid assembly of the [7−5−5] all-carbon tricyclic core common in the Daphniphyllum alkaloid family using an IPKR as a key step. In combination with a mild, efficient, and stereoselective carbon−carbon double-bond migration, essential to the construction of the DEF rings of daphnilongeranin B (**2**), we have demonstrated the versatility of the derived core. A further late stage regio- and stereoselective allylic oxygenation completed the synthesis of the model DEF tricyclic ring system of the biologically active daphniyunnine D (**3**).

Acknowledgment. We thank the EPSRC (Leadership Fellowship to D.J.D., postdoctoral fellowships to B.D. and F.S, and studentship to I.N.M. and J.W.W.), the EC [IEF to F.S. (PIEF-GA-2009-254068)], AstraZeneca (studentship to J.W.W.), and Syngenta (studentship to I. N.M.). We also thank Dr. Barbara Odell (University of Oxford) for NMR studies.

Supporting Information Available. Experimental procedures and characterization data for all novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(29) Sabol, M. R.; Wiglesworth, C.; Watt, D. S. *Synth. Commun.* **1988**, *18*, 1–12.

(30) The only product isolated from the reaction mixture was compound **22**. No other regio- or stereoisomers were observed. We attribute the low reaction yield to degradation of the starting material under the oxidative reaction conditions.